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EPIDEMIC ENCEPHALITIS IN JUTLAND

A CLINICAL SURVEY FOR THE YEARS 1952—54

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Since the Economo pandemic after the First World War, the occurrence of acute encephalitis in Denmark has apparently been sporadic and sparse. A survey of the frequency of this disease in part of the country during the years 1918—38 was published by Vestergaard (1949).

In recent years, at any rate during the past 5 years, acute encephalitis has appeared with increasing frequency in Jutland. The cases presented a variable clinical picture, and many of them took a serious course.

A review of cases occurring in Jutland during the years 1952—54 is given below. As the epidemiology and aetiology of the disease are obscure, the review is chiefly confined to a clinical description.

No survey is given of the many major and minor encephalitis epidemics, but a few are mentioned whose location or time of occurrence make them relevant.

In the late forties an encephalitis epidemic whose aetiology was not ascertained occurred in the western part of Sweden (Afzelius-Alm 1951).

On the other hand, in the great Austrian epidemic in 1953 a virus was detected which is related to the one producing the Russian spring-summer encephalitis. The virus is transmitted by insects, and the disease shows an accumulation during the summer months (Rischling 1955; Grinschgl 1955).

It should be mentioned that there was a considerable number of poliomyelitis cases in this country in 1952. At the same time, polio and coxsackie were found in Sweden, especially in Malmö, both diseases occurring in the same epidemic areas. On the whole, however, the number of cases was rather small (Johansson 1954).

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PERSONAL INVESTIGATION

In order to gain an impression of the total number of hospitalized patients with encephalitis in Jutland (population about 2 millions), we sent a questionnaire to all hospital departments to which such patients might be supposed to have been admitted. Having sorted out, as far as possible, cases of second and further admissions to other hospitals, a total of 503 patients remained, distributed over the three years as follows: —

1952 — 135 patients
1953 — 183 »
1954 — 185 »

It cannot be ruled out with absolute certainty that the case material contains a few patients counted more than once; on the other hand, as information is not available from eight small departments, the figures may no doubt be taken as minimum numbers.

Of the 503 patients, 152 were admitted to the Neurological Department of the City Hospital of Aarhus, and it is these 152 cases which are analyzed below.

This figure is probably a minimum number, as all the case records were studied on the basis of diagnosis index cards; about 20 per cent of the cases were excluded because a systematic scrutiny left us in doubt as to the reliability of the diagnosis.

Further cases af acute encephalitis are no doubt to be found in other diagnostic groups, for example those manifested by cerebral vascular attacks.

We endeavoured to select patients with lesions of the central nervous system appearing to be of infectious origin, apart from bacterial diseases.

In the selection, special attention was paid to evidence revealed in the past history or by physical examination and pointing in the direction of an infectious cause; in many cases it was necessary to make various investigations to exclude a different aetiology. Finally, the course of the disease often offered a valuable clue to the selection.

OCCURRENCE

Frequency.

The frequency of the disease in the three years appears from Fig. 1.

The patients were registered by the dates of their admission to the department. This mode of registration, which proved more practical than trying to fix the time of onset of the disease, should not give rise to any essential changes in the seasonal variation.

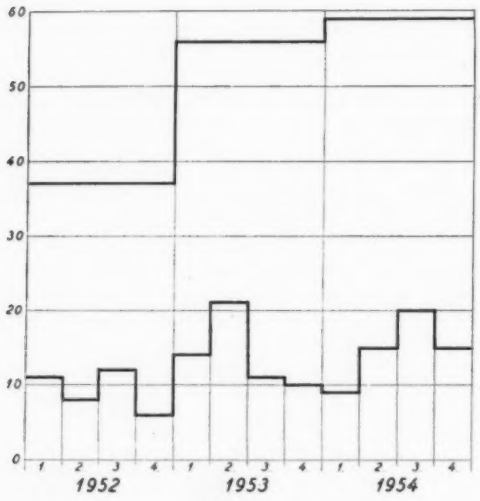

Fig. 1.

Abscissa: three-month periods of the years 1952—54. Ordinate: number of patients. The lower curve shows the number per three months, the upper curve the total number per year.

The cases thus occurred at all times of the year without any definite accumulations in any one season. On the other hand, the number of cases is seen to increase from year to year, and this trend seems to continue in 1955.

Sex and Age Distribution.

Of the 152 patients, 63 were females and 89 males.

The age of the patients on admission appears from Fig. 2.

There is a slight accumulation of cases in the age groups 0—10 and 30—40 years. As to the former group, it is not especially young infants who were affected, the age group 0—1 year comprising only three cases.

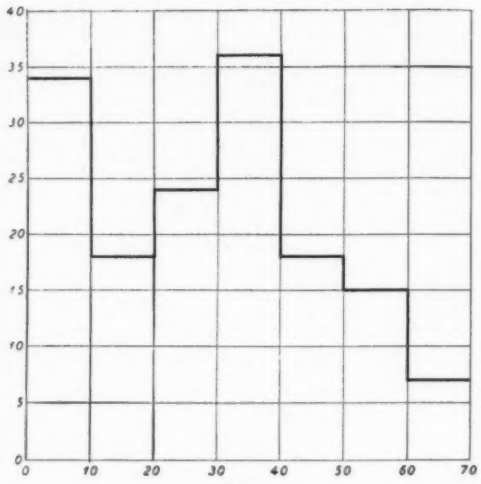

Fig. 2.

Abscissa: age on admission. Ordinate: number of patients.

Geographical Distribution.

The distribution according to the residences of the patients is shown in Fig. 3.

The frequency of encephalitis cases in the various parts of Jutland largely corresponds to the density of the population.

Of course, the local hospitalization possibilities have an influence on the number of patients admitted to special departments in the various districts.

EPIDEMIOLOGY

The geographical distribution of the encephalitis cases does not point to a definite epidemiological focus. It is true that the disease may present an epidemic picture, but it is impossible to decide whether one or several epidemics exist.

The following examples serve to elucidate the epidemiological aspect of the disease: —

Many of our patients informed us that simultaneously with the onset of their disease, febrile disorders had been present in their surroundings, often in a form believed to be influenza. It was often stated that cases of dizziness of a varying duration had occurred in the neighbourhood. The following investigation covering a population of about 2000 may be mentioned as an example of such a micro-epidemic. The investigation in the locality in question was undertaken 2 years after the epidemic.

Case 1. — A woman (F. 16717), aged 51 years, had a sudden attack of vertiginous spells in the autumn of 1953; there was a tendency to deviation towards the left in walking. A fortnight later paresis of the left upper and lower extremities developed; the paresis was pronounced a few days and then began to subside. For a short period the patient complained of diplopia.

Examination about eight months after onset of the disease revealed slight paresis of the left arm, a positive Babinski reflex on the left side, and a tendency to fall in the Romberg test. The spinal fluid was normal.

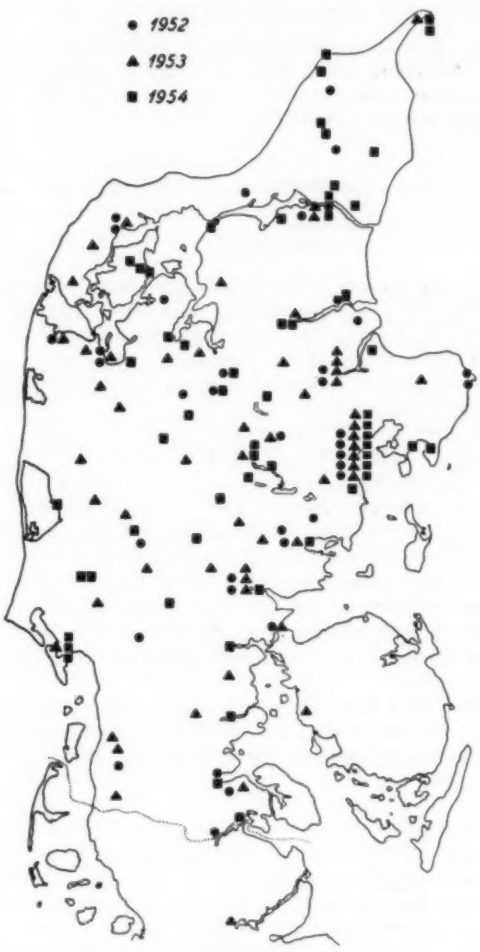

Fig. 3.
Residences of 152 patients with acute encephalitis. Different signs for onset in the years 1952—54, respectively. (Population of Jutland: approx. 2 million).

Since then the patient has steadily improved but, two years after the onset of the disease, has not yet completely recovered.

Case 2. — A woman, aged 38 years, fell ill in September, 1953, with symptoms suggestive of a common cold and a slight rise in temperature. The cold rapidly disappeared but was followed by pronounced dizziness and moderate pain in various joints. Progressive drowsiness developed. She was bedridden for a fortnight, during which period the drowsiness subsided. Since then pronounced fatigue and dizziness has intermittently been present (she has a sensation as if the head is pulled backwards). For a short period after the disease she had great difficulty in concentrating.

Two years after the onset of disease the patient has not yet completely recovered but still complains of episodes of fatigue and dizziness lasting for a few days.

Diplopia or paresis were never present.

Case 3. — A woman, aged 46 years, fell ill on November 9, 1953. A few weeks before she had paid a visit to the patient in Case 2, who was ill at that time. The disease started with symptoms of a common cold, and within a few hours pronounced dizziness developed. The temperature rose to 38.5° C., and the patient had to stay in bed for 16 days. During this period she was somnolent for several days and experienced visual hallucinations of an unpleasant nature. She complained of a sensation of heaviness, muscular weakness and numbness of the extremities on the left side. For a short period there was diplopia. The dizziness was very disturbing; the patient felt as if she was being drawn sideways; the conditions was aggravated when she turned her head, and when she closed her eyes, she had a sensation as if falling through empty space. At times there were associated attacks of nausea and vomiting.

The symptoms from the extremities and pronounced fatigue persisted for a period of 6 to 12 months. The dizziness, which was at first constant, gradually became paroxysmal and has now almost disappeared. Her memory and power of concentration are stille slightly impaired.

Case 4. — A woman, aged 32 years, fell ill with angina in August, 1953. She was bedridden for about a fortnight, then out of bed for two days, and again bedridden for about a month because of sensory changes in the limbs on the right side, accompanied by a feeling of heaviness in the right leg. The patient was markedly drowsy for 3 days; she could be aroused, but relapsed into somnolence as soon as she was left alone. There was no rigidity of the neck.

During a long period there were orthostatic disturbances and distinctly impaired concentration. For one year after onset there was pronounced dizziness with disturbances of equilibrium.

Two years after onset the patient has almost recovered.

Case 5. — A woman, aged 49 years, who, after the First World War, had a slight attack of uncomplicated influenza.

In September, 1953, a febrile disorder confined her to bed for three weeks. The most prominent symptom was dizziness, manifested by a sensation as if tables and chairs seemed to move up towards her. Other symptoms were diplopia, difficulty in concentrating and moderate headache. There was no paresis of the extremities.

Two years later the patient still suffers from paroxysmal fatigue of some hours' duration. During these attacks she turns greyish pale and becomes dizzy and nauseated, with a feeling of being drawn to the left. Two years after onset of the disease the dizziness may still be so pronounced that she has to support herself against a wall to prevent falling.

Just before the beginning of the disease the patient had been on a short trip to Norway to visit her sister-in-law. The latter developed a febrile disorder of seemingly cerebral origin a few weeks after the onset of our patient's illness. The circumstances seem to indicate that our patient transmitted the disease to her sister-in-law in Norway.

Case 6. — A woman, aged 34 years, had previously suffered from various diseases without relation to her present illness. Eleven years ago she had high fever associated with severe headache and stiffness of the neck, but no paresis. This disease was interpreted as poliomyelitis, and there were several similar cases in the neighbourhood. Since then she had felt tired and had often had headache.

In the autumn of 1953, symptoms like those of a common cold developed, accompanied by fever for a few days. Four days later muscular weakness of the lower extremities was noted, and on the fifth day she seems to have been drowsy. Later muscular weakness of both upper extremities and diplopia developed. During the early period of the disease the patient suffered from severe dizziness with disturbances of equilibrium, which symptom has now disappeared. The chief complaints are now a feeling of fatigue and insufficient working power; there are still attacks of headache. The symptoms are more pronounced than before the disease in 1953.

Case 7. — A boy, aged 8 years, fell ill in October 1953, with symptoms like those of a severe cold. He was bedridden for a fortnight. Dizziness was present for some days, and during a short period he was unable to stand on his legs. He is now perfectly well.

During the autumn of 1953, i.e. simultaneously with the seven cases just described, about 40 cases with dizziness as the principal manifestation occurred in the same district. The duration of the dizziness ranged from a few days to about 12 months. In some of the cases, the disease was ushered in by fever, and many of the patients complained of fatigue and difficulty in concentration.

During the period in question no cases of poliomyelitis were observed in the district.

Thus, in a population of 2000, nearly 50 cases were observed within a period of about 4 months, ranging in severity from somnolence and paresis to mild dizziness of a few days' duration. It seems reasonable to assume that these cases may have had a common aetiology.

The investigation demonstrates not only that the disease may occur in an epidemic form, but also that the aetiology of epidemic vertigo is probably identical with that of more serious cases of encephalitis.

As many cases of this epidemic vertigo have occurred in several regions of the country, the encephalitic infection must be supposed to have been fairly common. A considerable number of similar cases have also been observed outside Jutland.

Another example is the following: A man (F. 14367), aged 25 years, was admitted with encephalitis early in 1953. Six months later, incipient cerebral symptoms of slow progressive development were noted in the patient's 6-year-old son, who after the lapse of another six months was admitted to hospital with encephalitis manifested, inter alia, by bilateral papilloedema.

It can hardly be doubted that the aforementioned 503 hospitalized patients constitute only a minor proportion of the total number of persons who had acute infections of the central nervous system. Thus, in the above-mentioned epidemic only two of the approx. 50 patients had been admitted to hospital because of encephalitis.

SYMPTOMATOLOGY

The disease presented a highly variable picture. The following table shows a rough classification according to the parts of the nervous system which were especially involved.

	Cases
Encephalitis	116
Myelitis	27
Radiculitis	8
Choriomeningitis	1

The eight cases listed as radiculitis were cases in which radicular symptoms were predominant. Some of the patients also exhibited signs of involvement of the spinal cord. In the cases of pure radiculitis it is unknown whether the disorder is of infectious or toxic origin.

A division of encephalitis into the classical groups — cortical, subcortical, pontine, etc. — is not considered convenient, as only a minority of the cases fit entirely into any one of these groups. In the said system, the subcortical group would be the one represented by the greatest number of cases, the series comprising eight cases of fairly pure hemiplegia. The syndrome encephalomyelitis funicularis infectiosa (Munch-Petersen 1934) was represented by six cases under the diagnosis of myelitis.

Instead, I have chosen to give a survey of the most prominent subjective and objective symptoms accompanied by some illustrative case reports.

	Cases
Fever	51
Headache	49
Vertigo	43
Sensory symptoms	50
Paraesthesiae	43
Coma	17
Clouding of consciousness	17
Epilepsy	23
Mental symptoms	26
Paresis	81
Paresis of eye muscles	30
Papilloedema	31
Defects in the field of vision	5
Involuntary movements	17
Various otological findings	35
"Decerebration"	4

Table 1. — The most prominent subjective and objective symptoms in 152 patients; cf. text.

Fever was expressly stated to be present only in about one third of the cases; in many of these cases the disease had primarily been interpreted as influenza.

Dizziness was a frequent and often very troublesome compiaint, but vertigo alone was rarely seen in the patients; the dizziness will be described in greater detail in connection with a case report.

Loss of consciousness was seen in 17 cases. The unconsciousness lasted from a few hours to a few weeks; we saw a single instance in which unconsciousness persisted for 5 weeks. Other changes of consciousness, *viz.* torpidity and somnolence, were observed in 17 cases. Epilepsy assumed to

have been caused by encephalitis was encountered in about one sixth of the patients. Of the 23 patients with epilepsy, 13 were children under 10 years of age.

Unquestionable mental symptoms were present in 26 patients, including six with dementia, three with pronounced organic reduction, and two with hallucinations. Besides, the group included patients with severe behaviour disturbances and a markedly impaired power of concentration. Mild cases of weakened concentration were not included.

There were 81 cases of paresis (apart from paresis of the eye muscles), *viz.*, a few with monoplegia and eight with hemiplegia, while the remaining cases presented mixed pictures.

Thirty patients showed paresis of the eye muscles; four of these were associated with unconsciousness, a combination suggesting Economo encephalitis.

Papilloedema was observed in 31 patients, a remarkably large number, since papilloedema has previously been found only very rarely in encephalitis patients. During the epidemic after the First World War, some cases were observed in this country (Winther 1927), but since then it has been a rare occurrence. In some of the patients papilloedema was the only objective finding; as a rule they had had obscurations, but otherwise felt perfectly well. A case report on a patient with papilloedema is reported below and, besides, the reader is referred to a paper by J. H. Rasmussen.

Otological symptoms were found in 35 patients. The most frequent finding was nystagmus, in some cases accompanied by directional preponderance, and a few patients revealed slightly impaired hearing. Here it should especially be noted that in the patients with pronounced dizziness, tests for vestibular function showed equal reaction on both sides.

The group "decerebration" represents a particularly serious picture of disease, which is illustrated below by a case report.

Case 8. — A boy (F. 17054), aged 12 years, was admitted in August 1954. Up to that time he had essentially been in good health.

During the last six months prior to admission a mental change had occurred; he became progressively sleepy, would at times give an impression of absent-mindedness, and often showed choreiform movements. Later, there were twitchings in the left arm many times during the day. At first the condition was conceived as "nervousness".

Progressively increasing dizziness developed, and his sleep requirements became so conspicuous that he was able to fall asleep at any time. Incoördination of the extremities on the left side developed, and there were also obscurations. Bilateral papilloedema was observed, for which reason the patient was admitted to the Neurosurgical Department. Examination revealed slight hemiplegia and incessant jerks in the left upper and lower extremities as well as on the left side af the face. There was impaired vision of both eyes (6/24), as well as bilateral papilloedema of 2 dioptres, but only questionable venous stasis.

Ventriculography revealed a pressure of 450—550 mm of water; the ventriculograms showed normal conditions.

The patient was tranferred to the Neurological Department. Lumbar puncture showed a pressure of 200 mm of water, 2093/3 cells, globulin 5, albumin 52 (Bisgaard). The Wassermann reaction was negative. The collargol curve showed initial precipitation. The suprarenine-cerebrospinal-fluid-sugar test was 0.069 (abnormal). The Weil, Widal, Paul Bunnell, Q-fever complement fixation, and parotitis complement fixation tests were negative. Haematological examination revealed no abnormalities.

About 6 months after the onset of the disease the patient had epileptic attacks manifesting themselves as grand mal seizures and later as unconsciousness of short duration with a single violent jerk in all extremities. The latter attacks gradually became very frequent and for a time occurred at intervals of a few seconds. In the course of time his electro-encephalogram became markedly abnormal, with frequencies of 2—3 per second and a considerable increase of voltage; in the intervals between the bursts of high voltage there was only little electric activity (see Fig. 6, which shows a typical section of the E.E.G.).

During the same period a considerable, but somewhat fluctuating, rigidity developed in all extremities, and the patient often lay in the opisthotonos position. He exhibited various mental symptoms, such as compulsive crying and laughter, and in the course of 6 months dementia developed. He has now lived with his disease for about 18 months; he lies in a state of blindness and continues life at a merely vegetative level. He is hypokinetic and has no contact with his surroundings. He is incontinent of urine and faeces. His somatic condition is good.

For diagnostic reasons cortex biopsy was undertaken. Part of the biopsy specimen was subjected to histological examination, and the rest was sent to a virus laboratory in Sweden for examination. No virus was demonstrated.

Histological examination of the biopsy specimen from the parietal lobe of the brain was performed by Dr. Munch-Petersen. Leptomeninges: the pia-arachnoid was slightly fibrotic, with mild lymphocyte infiltration. Cortex: diffuse shrinkage. Variable shrinkage of the ganglion cells was observed. The shrinkage was most pronounced in the deeper layers of the cortex. Here, progressive glial changes were also observed.

In the subcortical tissue there appeared to be total degeneration of the medullary sheaths. The degeneration included Meynert's U-fibres. There was very marked proliferation of protoplasmatic astrocytes; the cytoplasm was greatly increased. The nuclei were eccentrically placed, often with a distinct nucleolus, occasionally with several nucleoli. The cells showed syncytial processes.

Perivascular findings were: pronounced round-cell infiltration and numerous microglia cells showing considerable fat accumulation. The astrocytes also contained fat. The vessel walls showed round-cell infiltration.

Inclusion bodies were not demonstrated.

Histological diagnosis: leuko-encephalitis.

The patient suffers from the so-called Dawson encephalitis. The course is characteristic. Generally, the disease passes through three stages. The first stage is characterized by symptoms resembling "nervousness", and epileptic attacks are a frequent occurrence. At the second stage the patient is often stuporous and affected with complicated extrapyramidal disturbances, frequently of a fluctuating nature. At the third stage the patient gives the impression of being decerebrate; there are blindness and quadriplegia, and the involuntary movements subside. The electro-encephalogram of this patient was typical of the disorder, and the same is true of the histological findings, even though no inclusion bodies were observed.

The duration of the disease generally varies between 2 and 6 months, but there is probably also a chronic form.

In my opinion, the present case material comprises four cases of Dawson encephalitis.

The disease has been described with increasing frequency during recent years (Dawson 1933; Brain, Greenfield, Russell 1948; Greenfield 1950). In all probability, it is identical with the type described by van Bogaert (1956, 1953).

Case 9. — This patient (F. 18186) is not included in the case material, because she was admitted in 1955, but as the case history is illustrative, it is nevertheless reported here.

The patient was a woman, aged 20 years, who had a single convulsive attack at the age of 2 years, as well as vague nervous complaints.

On the evening prior to admission she felt indisposed, and complained of headache and pain in the nape of the neck as well as in the joints. The next morning she rose as usual, but an hour later she was found unconscious, and convulsive seizures were observed.

On admission to the Medical Department, she was febrile and somnolent. She responded only weakly to pinpricks, but it was not possible to establish contact with her. There were undulatory nystagmus, bilateral Babinski response and some fasciculations in the left lower extremity. Spinal fluid: pressure, 180 mm of water; 148/3 cells, the majority of which were mononuclears.

The patient was transferred to the Neurological Department and lay in a state of somnolence for two days; then she began to become reactive, responding with a few words to questions. On the fifth day she gave a psychotic impression; she talked to imaginary persons, had hallucinations and was disoriented as to time and place. On the next day she appeared completely normal and felt well.

About a week later, peripheral facial palsy developed, probably due to a nuclear affection. The facial palsy disappeared when electrotherapy was given, and the patient was discharged without symptoms.

A cortical biopsy specimen revealed no virus.

Histological examination of cortical tissue (Munch-Petersen): Degeneration of the ganglion cells, perivascular round-cell infiltration and oedema of the white substance (acute encephalitis).

On admission for re-examination 5 months later, the patient stated that she was perfectly well, and physical examination showed no abnormalities.

Case 10. — A woman (F. 14709), aged 47 years, was admitted to this hospital from April 9 to May 22, 1953. A fortnight prior to admission she had a sudden attack of severe dizziness and frontal headache accompanied by vomiting. A few days later she had double vision of the horizontal type, and after another few days clouding of consciousness developed. She slept most of the time; at first she could be aroused, but the clouding increased, and the patient lapsed into unconsciousness for a few hours.

On admission here, she appeared markedly oligomimic and sluggish as regards spontaneous movements. She walked slowly, almost without movements of the arms. Otherwise, physical examination revealed no abnormalities. The spinal fluid was normal. The appearance of the patient had completely changed since before her disease.

On re-examination two years later she was still sluggish, stagnant and oligomimic, but there was no tremor. Her complaints were suggestive of a neurastheniform condition.

Thus, Parkinsonism seems to have developed in this patient in the course of a few weeks.

Cases 9 and 10 may serve to elucidate the question of Economo encephalitis (see e.g. Economo 1929). The fact that Case 9 showed clouding of consciousness of rather acute onset, and that a Parkinsonian picture soon developed in Case 10, seems to indicate that these cases should be classified as Economo encephalitis. It has been a subject of discussion as to whether this type still exists after the cessation of the pandemic about 1925. It is impossible to prove that it was the same disease, since the aetiology of Economy encephalitis is unknown. The clinical pictures are so much alike that it must be justified to assume that ours were of the same type. We have seen Parkinsonism develop in several patients, including some children, and the picture is not uncommon.

Case 11. — A woman (F. 17741), aged 22 years, was admitted to hospital from December 15, 1954, to March 15, 1955. She had formerly shown vague neurotic symptoms but had otherwise been in good health.

About 3 months prior to her admission in 1954, a feeling of intense fatigue and muscular weakness of the lower extremities without preceding illness developed. For a period of about 2 months she had attacks of headache, which were sometimes accompanied by nausea, but never by vomiting. During these spells she had flickering before the eyes and blurred vision.

On admision to the Neurosurgical Department, vision was found to be normal, but ophthalmoscopy showed bilateral papilloedema of 3 dioptres, obliterated margins of the discs, and a few haemorrhages and exudates; the arteries were slightly narrowed and shining.

Neurological and otological examinations showed normal conditions. Electro-encephalography: a slightly abnormal curve without special characteristics or focal changes. Arteriography of the right carotid showed nothing definitely abnormal. Ventriculography revealed a pressure of 290 mm of water and very slight dilatation of the lateral ventricles; otherwise nothing abnormal.

The patient was transferred to the Neurological Department where she remained for 3½ months. The papilloedema first increased up to 4 dioptres, and then gradually subsided; at discharge, it was 2 dioptres, and

on re-examination 8 months later less than 1 dioptre. Throughout the period the acuity of vision was normal (6/6). Apart from the visual complaints the patient felt perfectly well.

Later, ventriculography was again undertaken and showed unchanged conditions; arteriography of the left carotid revealed normal conditions; there was no pleocytosis of the ventricular fluid. Serological examinations showed nothing abnormal (Weil, Widal, Paul Bunnell); however, a stationary reaction was found for leptospirosis (canicola and Sejrø), but these reactions are hardly of relevance.

This patient represents one of the 31 cases characterized by papilloedema, a type that is rather common. Patients of this kind have, on the whole, only visual complaints, and otherwise feel completely well.

The duration of the papilloedema of these patients varied greatly, up to several years. A few patients were affected with extensive disturbances in the field of vision, but in most cases these changes proved to be remarkably regressive. Temporarily impaired vision occurred in some cases, but in a strikingly large number of the patients the visual acuity was normal.

Case 12. — A woman (F. 17135), aged 30 years, was in hospital from August 21 to September 4, 1954. Her past history was that of good health. Her indulgence in tobacco was moderate and she did not drink alcohol.

Five weeks prior to admission vertiginous spells of sudden onset began. The dizziness became aggravated during the first few days, was highly discomforting for 2—3 weeks, and then began to subside. On admission, dizziness was present only when the patient lay on her back with closed eyes. During the first few days of illness she vomited repeatedly, and complained of slight diplopia on gaze in all directions and tingling of the left cheek.

Otological examination one week after the onset of the disease had shown spontaneous horizontal-rotatory nystagmus towards the left.

There was no fever, tinnitus, impairment of hearing or difficulty in concentration.

On admission, neurological examination showed no abnormalities. There was slight nystagmus on lateral gaze. Psyche: normal. Ophthalmological examination: nystagmus on the lateral gaze, most pronounced to the right. Visual acuity, ophthalmoscopy and perimetry showed normal conditions. Otological examination: no spontaneous nystagmus. Calorigram and audiogram were normal. Roentgenograms of the skull were normal. Spinal fluid: pressure, 360 mm of water, 12/3 cells, globulin 1—2, albumin 18; Wassermann reaction negative. Blood pressure 120/80.

Dizziness was the predominant symptom in this patient. In the total series there were 43 patients in whom dizziness was a conspicuous symptom. Cases of monosymptomatic dizziness and absence of neurological abnormalities were rare.

In this country, Borberg (1947) described epidemic vertigo as a form of encephalitis. Winther (1952) published a report on a comprehensive case material and a survey of the literature. He expressed the opinion that the disease was actually encephalitis, which view, however, Mygind (1952) could not accept.

Our case material suggests that the syndrome is a type of encephalitis. As already mentioned, we found, in the same epidemic, a gradual transition from severe forms of encephalitis (paretic-somnolent) to cases of dizziness of a few days' duration. Besides, patients who on examination exhibited no symptoms other than dizziness often appeared to have had other mild neurological manifestations such as paraesthesiae, diplopia, etc.

The clinical manifestations observed in the patients — both in and outside hospital — particularly suggest that the disease, as it appears at present, is ushered in by dizziness of acute onset, usually without fever in the initial stage and often associated with frontal headaches and difficulty in concentrating. At first the dizziness is constant; later it occurs in paroxysms, often persisting for days. During these spells the patient is very tired and often extremely pale. Feeling of insufficiency, emotional dejection and anxiety often develop in the course of the disease.

The disease may persist for several years, but will in most cases subside within about two months.

A considerable number of cases of this disease have occurred, and it does not seem to have been confined to Jutland alone.

In addition, there have been many cases of dizziness of short duration in which the initial symptoms were of a gastro-intestinal nature. This condition presents an entirely different picture and is of very short duration; in all probability, its aetiology is unrelated to that of epidemic vertigo.

The discussion of the various differential-diagnostic considerations (excessive smoking, ear affections, epilepsy, neurosis, etc.) is outside the scope of this paper.

LABORATORY EXAMINATIONS

Cerebrospinal Fluid.

0—10/3 cells	84
10—20/3 cells	19
Over 20/3 cells	46
Albumin 0—15	39
» 15—30	59
» over 30	35
Cerebrospinal pressure $\leq$ 200 mm of water	91
» » $>$ 200 » » »	44

Table 2. — Composition of the spinal fluid.

We have fixed the limit of normal cerebrospinal pressure at 200 mm of water (patient in recumbent position). In 17 patients it was impossible to determine the pressure with certainty; these were mostly children who were crying and excited during the lumbar puncture.

The cells were mainly mononuclears.

Protein determination was performed by the Bisgaard method. Protein values are not available in all cases, because determination was impossible, chiefly due to admixture of blood, which often

occurred, when the fluid was withdrawn in relation to ventriculography.

The combination of a cell count under 10/3 and an albumin value under 15 was found in 34 patients. This combination represents what we call — or at least used to call — a "normal spinal fluid". As mentioned above, we have previously fixed the border value of normal spinal fluid at 10/3 cells and an albumin level of 15. However, in recent years we have observed a change in the composition of the spinal fluid.

To throw light on this change, we have analyzed the cell counts and albumin values for all spinal fluids examined in our department during the years 1952—54, i.ee., more than 5000.

The results are shown in Figs. 4 and 5.

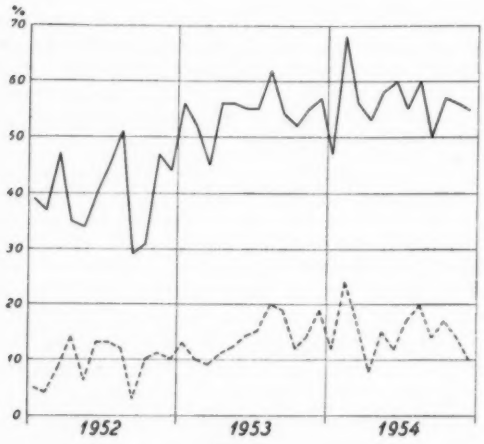

Fig. 4.

Albumin values (Bisgaard) for the total number of spinal fluids examined in the department during the years 1952—54, made up per month (abscissa) in percentages of the total number (ordinate). The solid curve indicates albumin values over 15, the dotted curve albumin values over 30.

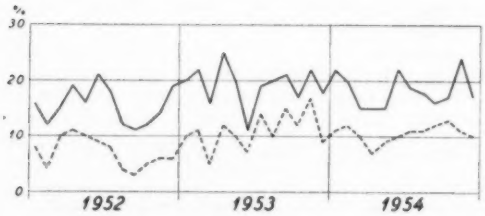

Fig. 5.

Showing the corresponding cell counts (cf. Fig. 4). The solid curve indicates cell counts over 10/3, the dotted curve counts over 20/3.

For comparison, we may mention the figures for the total number of spinal fluids examined in 1945 (about 1300). In this material, 20 per cent showed cell counts over 10/3 and 29 per cent albumin values over 15.

While the cell counts are unchanged, the number of spinal fluids with increased albumin content has risen considerably; for 1952—54 the percentage of fluids with increased albumin is about twice as large as that for 1945.

The cause of this change may be that the exposure of neurotropic infection has been more massive during recent years, but there are other possible explanations. The changes are hardly due to changes in laboratory technique.

As is well known, the Bisgaard method is beset with a certain amount of inaccuracy. It should be noted, however, that our department has twelve years' experience in the use of the method, so it can hardly be doubted that the aforementioned change in the spinal fluids is a reality.

The suprarenine-cerebrospinal-fluid-sugar test of the spinal fluid was performed on 73 of the patients. In 34 patients it was normal, in 39 abnormal. An abnormal reaction suggests a hypothalamic lesion (Munch-Petersen 1937, 1950).

The *sedimentation rate* was found to be under 15 mm/hr. in 118 patients; in 19 patients it was over 15 mm/hr., but for at least 7 of these there are other possible explanations of the increase, particularly pyuria.

Electro-encephalography. — For patients with Dawson encephalitis we found electro-encephalograms typical of that disease. (Radermecker 1949; Cobb & Hill 1950; d'Avignon, Husby & Widén 1954).

Slow waves with high voltage were observed, often occurring regularly. In the intervals between the paroxysms there was only very little electric activity.

The electro-encephalograms for encephalitis patients in coma showed changes typical of comatose patients.

Electro-encephalograms were recorded for another 97 patients, but the recordings were not made at a definite time in relation to the onset of the disease. The E.E.G. was normal in 37 patients and abnormal in 60. It should be noted that the finding of an unspecifically abnormal E.E.G. need not necessarily imply that the abnormality is a consequence of the encephalitis of the patient.

The abnormalities observed were of an unspecific nature; they consisted in an increase in the occurrence of low frequencies. In 52 cases the changes were moderate, increased occurrence of potentials down to 5 per second being observed. In 8 cases there were pronounced changes, with frequencies as low as 2—3 per second. In 18 cases focal changes were observed.

In 9 cases it was shown with certainty that a relevant change of the E.E.G. occurred during the disease, i.e. the E.E.G. approached normal, parallel with the clinical improvement. One patient, however, showed aggravation of the condition and increasingly abnormal E.E.G.

Seroreactions. — The Weil, Widal and Paul Bunnell tests were performed on many of the patients, and some were tested for Q-fever, toxoplasmosis and parotitis. No definite abnormalities were re-

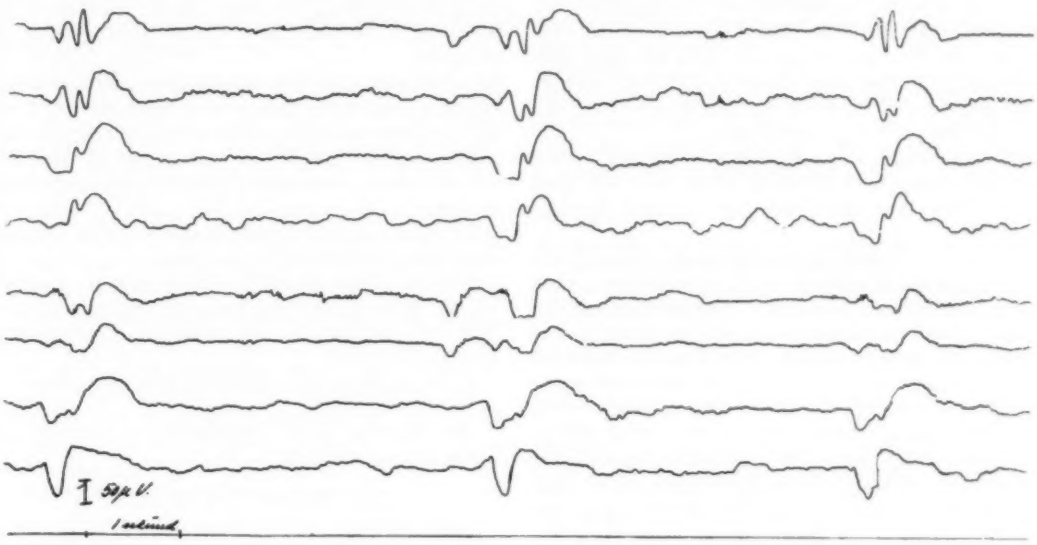

Fig. 6.
E.E.G. for a patient with Dawson encephalitis (F. 17054).

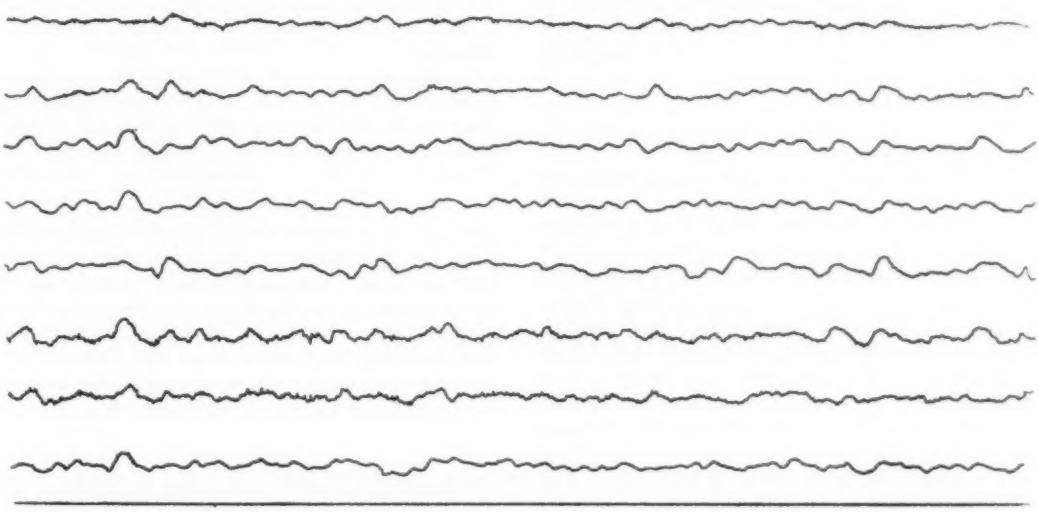

Fig. 7.
E.E.G. for a patient with acute encephalitis and unconsciousness of five weeks' duration. The curve was recorded in the comatose phase (F. 15948).

vealed apart from a positive reaction for Brucella abortus Bang. A number of other serological examinations would have been desirable, but were not possible.

Other Examinations.—Encephalitis may be easily recognised, but it may also cause diagnostic difficulties, for which reason it may be necessary to make thorough investigations to exclude other disorders. It may be mentioned that roentgenograms of the skull were taken in 118 cases; arteriography was performed in 34, and ventriculography in 46 cases. The ventriculograms were normal in 18 cases, while a variable degree of mostly mild atrophy was present in 18 cases.

Virus Examination. — In a minority of cases, attempts were made to cultivate virus from biopsy specimens of the cortex, always with a negative result. Our facilities for virus cultures were not so good as would be desirable; thus, we were unable to make routine examinations for coxsackie.

Haematology. — Peripheral blood and sternal marrow were examined in many of the patients. In

some of them the sternal marrow appeared to contain cells characteristic of infectious mononucleosis. Examination of the peripheral blood for these cells revealed that they were more frequent here than in the marrow, which seems to indicate that the cells are formed in the lymphoid tissue.

Mononucleosis cells are usually divided in 3 types (McKinlay & Downey 1953), and the type found here was most like the so-called Downey Type II.

The cell we found was rather large, resembling a big lymphocyte containing a large nucleus with fine threads and a delicate chromatin structure, usually without distinct nucleoli. The nucleus was round or kidney-shaped, and slightly indented. There were abundant amounts of moderately basophilic cytoplasm. It showed a characteristic undulating boundary, which was clearly visible only in the thinnest portions of the smears. In the periphery there were areas showing more pronounced basophilia, which was probably due to the cell's being "rolled up", i. e., double in places. The cell differs from Downey II in that the nucleus of the latter usually has larger flakes of chromatin granules. These cells are not specific for infectious mononucleosis, but have been described in a number of vira infections (hepatitis, measles, rubella, influenza, zoster, etc.). In fact, it has been suggested that the cell be called "virocyte" (Litwins & Leibowitz 1951).

In normal adults, these cells are extremely rare and never exceed 1 per cent.

The haematological examinations in which this type of cell was revealed in our patients were made by J. Bichel, who will publish a more detailed report when more experience has been gained.

A special perspective is given to the above finding by the fact that the same cell type has been detected in some of our patients with disseminated sclerosis. This opens the possibility of future findings which may bridge the gap between certain forms of encephalitis and certain forms of disseminated sclerosis. Thus, the detection of this cell may be of importance in a subdivision of disseminated sclerosis which has been aimed at by many investigators (Munch-Petersen 1955, and others).

TREATMENT

The treatment, which varied very much, was largely symptomatic. In the comatose patient it was achieved by suction and physiotherapy to prevent atelectasis. In some patients, tracheotomy and oxygen treatment were necessary. In these cases measures were taken to prevent disturbances in the fluid balance.

Antibiotics (penicillin, Aureomycin, etc.) were employed to a certain extent in a large proportion of the cases to prevent secondary infection. Intensive iodine treatment was given to 30 patients. During the Economo pandemic iodine therapy was used, according to the reports with good effect. Usually, a maximum of 65 g of sodium iodide was administered intraveneously in the course of 11 days, but a definite effect of this therapy was not obtained.

In some cases antihistaminic drugs administered in large doses for several weeks were given a trial (particularly in patients with monosymptomatic papilloedema and in patients with a history of allergic reactions). No effect of this treatment was observed.

In some patients with long-continued disease hypertherm treatment was given.

Finally, physiotheraphy was used to a great extent, at the acute stage frequently as a preventive measure, and later in the disease in the re-education of the patient.

In the patients with dizziness, Bellergal proved to give the best effect.

We attached great importance to a prolonged convalescence period.

COURSE OF THE DISEASE

It is still too early to estimate the course of the disease, as the observation period is too short. We know that at least seven of our patients have died, while six have shown such progression of the disease that the prognosis is bad. Improvement has occurred in 85 patients and seven are free of symptoms.

The figures just cited are based on the conditions at discharge, on admission for re-examination in some cases and, finally, on answers to questionnaires sent to about one sixth of the patients.

AETIOLOGY

In the series, encephalitis followed measles in one case and rubella in one; two had zoster myelitis, and one case of encephalitis was possibly caused by Brucella abortus Bang. In the remaining cases the aetiology is unknown, but we believe that their encephalitides were due to viral infection.

In the few cases in which attempts were made to cultivate virus no growth was observed.

SUMMARY

During the past 5 years acute encephalitis has occurred with increasing frequency in Jutland (population about 2 million). The present paper gives a clinical review, for the years 1952—54, of patients suffering from diseases suggestive of infection of the central nervous system. A total of 503 patients were admitted to hospitals in Jutland with such complaints, but there must, no doubt, have been a considerably greater number of non-hospitalized patients.

A series of 152 patients were admitted to the Neurological Department in Aarhus; a more detailed description is given of this series.

The disease shows no seasonal variation, but there is a slight rise in the frequency from year to year. Of these 152 patients, 89 were males and 63 females. The affection occurred in all age groups, but there was a slight preponderance in the two

groups 0—10 and 30—40 years. Geographically, the frequency corresponds fairly well to the density of the population.

The disease may appear in an epidemic form. An epidemic in which 50 cases were observed within 4 months in a population of 2000 is reported. The severity of these cases ranged from deep coma to dizziness of a few days' duration.

This epidemiological observation correlated with the occurrence of all intermediate gradations from mild to severe clinical manifestations suggests that epidemic vertigo is a type of encephalitis.

The clinical picture varied within wide limits, and the disease often took a serious course. The most conspicious symptoms appear from Table 1. is noteworthy that there were many cases of papilloedema and impaired consciousness. The case material comprised 4 cases of Dawson encephalitis and a few patients exhibiting a clinical picture resembling that of Economo encephalitis.

The composition of the spinal fluid is seen in Table 2. Less than one half of the patients had pleocytosis, and more than one half showed albumin values over 15 (Bisgaard). In most of the patients, the cerebrospinal pressure was under 200 mm of water.

The sedimentation reaction was found to be normal in the majority of the cases. Serological examinations showed nothing of particular importance. Electro-encephalography revealed typical changes in patients with Dawson encephalitis. In some cases, the electro-encephalogram showed unspecific changes.

In a few cases, attempts were made to reveal virus on culture, but there was no growth.

In a fairly great number of the patients the sternal marrow and, to a higher degree, the peripheral blood, contained a cell resembling the Downey Type II. This cell type is fairly common in patients suffering from virus diseases. We have also observed it in some of our patients with disseminated sclerosis.

The treatment was symptomatic. In addition, iodine, antihistaminic drups and antibiotics were administered, but no definite effect was obtained.

The aetiology is unknown. The disease is likely to be due to a viral infection.

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INDUCED HYPOTENSION BY SPINAL ANALGESIA

By SOPHUS JOHANSEN and VIGGO DYRBERG

As early as 1901 (Morton) and 1902 (Payne), high spinal analgesia was used for operations on the head and the neck. Neither these authors nor later workers such as Pitkin (1928) and Koster & Kasman (1929) utilized this technique for hypotensive purposes, but they realized the presence of hypotension and reduced bleeding.

Als-Nielsen (1935) discussed the causes of the fall in blood pressure that may occur in spinal analgesia and supported Tuffier's (1901) early theory that hypotension was caused by paralysis of vasoconstrictor nerves in the subarachnoid space.

Vehrs (1931) has demonstrated that weak solutions of procaine in spinal fluid prevent conduction of impulses in sensory nerves but leave conduction in motor nerves intact. Sarnoff & Arrowood (1946) demonstrated that still weaker concentrations of procaine produce a universal paralysis of vasoconstrictor nerves (the sympathetic outflow from the spinal medulla), leading to a decrease in blood pressure, in the presence of unimpaired impulse conduction in sensory and motor nerves.

From the Department of Anaesthesia, Copenhagen County Hospital, Gentofte. Head: *E. Wainø Andersen.*

In the search for techniques that would reduce bleeding during operations, Griffith & Gillies recognised the opportunities implied by these investigations and introduced high spinal analgesia (so-called total sympathetic block) with the primary purpose of producing hypotension during surgical procedures.

During a period of two years we have had occasion to employ this method in 19 cases.

TECHNIQUE

During the operation the patient should be unconscious, as psychological factors and conscious activity may disturb the unphysiological state produced and render it difficult to control. Accordingly general anaesthesia is induced, usually by means of thiopentone 500—700 mg. When a free airway is secured, the patient is placed on his side, and spinal analgesia is applied in the usual manner through lumbar puncture. Hyperbaric solutions of local anaesthetic drugs are employed: procaine (150—200 mg in 3—4 ml of spinal fluid), tetracaine 1:100 (15—20 mg), or nupercaine 1:200 (7.5—11 mg), according to the intended duration of the hypotensive period. Immediately afterwards the patient is turned on his back and placed in a 30 degrees Trendelenburg position. After 10—25 minutes, varying with drug, injected dose and volume, and position of the patient, the systolic blood pressure drops to 70—80 mm Hg. As mentioned above, the blood pressure fall is due to a vasodilatation mainly affecting the small arteries and arterioles (Zweifach 1949) or, in other words, to the fact that the capacity of the vascular bed is increased, whereas the blood volume remains unchanged. As the blood pressure is a function of the cardiac output and the peripheral resistance, which mainly depends on the arterioles, the blood pressure decreases as the peripheral resistance is reduced. When the blood pressure has reached a level of 70—80 mm Hg, the table is raised to a slight head-down position and, if compatible with the surgical procedure, the legs of the patient are lowered. Vasomotor activity now being abolished, the blood tends to pool in dependent parts of the body, thus creating in the lower extremities a reservoir of blood that can be easily mobilized, if required, by raising the legs. Likewise, the surgical field is raised as far as possible relative to the rest of the body to further assist in the reduction of circulation in the elevated part. When the legs are lowered, the blood pressure usually falls another 10—20 mm Hg. Head-up position is warned against by Gillies (1952), as this increases the possibility of cerebral ischaemia. We consider the optimal blood pressure level to be between 60 and 80 mm Hg systolic, depending upon the patient's posture and age. Should hypotension below the desired level occur, and it cannot be corrected by altering the position of the patient, we inject small doses of vasopressor drugs. The operation is not allowed to start until the blood pressure is steady. Loss of blood during the operation should be replaced as accurately as possible, lest vascular filling be too poor to maintain adequate perfusion of the tissues.

Before the operation is finished, the patient's blood pressure is slowly raised to normal or subnormal levels by elevating the legs and, if necessary, by means of vasopressor drugs, to make certain that all bleeding vessels are properly dealt with. It is of the greatest importance that all bleeding points are carefully tied during the whole procedure if the method is to be successfully employed.

Transportation of the patient from the operating table to the bed should take place with as little change of the patient's posture as possible, since vasomotor mechanisms, as a rule, are still partially compromised. The foot of the bed is elevated slightly. Blood pressure, pulse and respiration are checked at frequent intervals in the immediate postoperative period. If the blood pressure has not been effectively raised at the end of the operation, the patient is given supplementary oxygen.

For abdominal operations the spinal analgesia in itself ensures perfect analgesia and muscular relaxation, so a very light general anaesthesia is sufficient to keep the patient asleep. If the larynx and trachea are anaesthetized topically previous to intubation, nitrous oxide in a 60 per cent mixture with oxygen is usually adequate. Cyclopropane has also been used for maintenance of the anaesthesia. The oxygen content of the anaesthetic mixture has in every case been considerably greater than that of atmospheric air. Maintenance of the anaesthesia by means of repeated doses of thiopentone is advised against (Gillies 1952), as the depressing action of this drug is badly tolerated under these circumstances.

The hyperbaric solution used for the spinal analgesia moves cephalad in the subarachnoid space after injection and becomes more and more dilute as it mixes with the spinal fluid. Consequently, motor nerve paralysis is limited to the abdominal and lower intercostal muscles, which again means that spontaneous respiration is sufficiently effective to ensure adequate ventilation of the lungs. Some importance is attached to the preservation of spontaneous breathing, partly because controlled respiration tends to diminish the venous return to the heart and thus the cardiac output, partly because changes in the character of the respiration during the hypotensive period may be the first indication of cerebral anoxia (Gillies 1952).

Anaesthetic apparatus that offers as little resistance as possible to respiration should be chosen, when this technique is to be employed, as an unhampered respiration and effective elimination of carbon dioxide both assist in

reducing venous blood pressure and thereby bleeding. A to and fro rebreathing system with carbon dioxide absorption has most often been used, but a Bullough's (1952) T-piece arrangement or a non-rebreathing valve, such as constructed by Ruben (1954) among others, offer added advantages.

With a total sympathetic block, the heart rate is slow owing to increased vagal influence. This leads to better cardiac filling during the prolonged diastole in spite of the diminished venous return to the heart. (Gillies 1952).

It can hardly be over-emphasized that a patient whose circulatory compensatory mechanisms are abolished through induced vasomotor paralysis should be kept under close observation during the entire hypotensive period, and any deviation from the intended clinical condition should be corrected immediately.

RESULTS

Our material (Table I) comprises 19 patients, who have undergone surgical procedures known to be difficult because of excessive bleeding. 15 patients were under 50 years of age. The general condition of the patients has been assessed as good. The existence of cardiac, vascular or renal disease has as far as possible been excluded beforehand by preoperative examinations. There have been no contraindications to spinal analgesia per se.

The systolic blood pressure has been on an average about 65 mm Hg. The duration of the hypotension has averaged 90 minutes, ranging from 25 to 190 minutes. The time taken before the desired blood pressure level was reached was prolonged in cases Nos. 1, 7, 10, and 12 (60, 50, 40, and 40 minutes). In three of these patients satisfactory hypotension was finally obtained, but in the remaining case (No. 10) the blood pressure could not be made to fall below 80—90 mm Hg. In the rest of the patients hypotension occurred after 10—30 minutes, on an average after 21 minutes.

At the end of the operation the blood pressure has been elevated by raising the legs and, in cases where this proved inadequate, by intravenous injection of a vasopressor drug. Methoxamine (Pressomin GEA) has been used for this purpose in 12 patients, ephedrine in one.

The patients have all been awake at the conclusion of the operation.

Bleeding has been noticeably reduced, but no attempt has been made to measure loss of blood. The surgeons have had the impression that hypotension improved operative conditions, particularly in the 16 Meigs' operations for carcinoma of the cervix uteri, where effective gland dissection is jeopardized by constant oozing from the richly vascularized field. The number of blood transfusions (of 500 ml each) administered during and after operations appears from Table I.

There have been no deaths. There have been two cases of postoperative ileus following Meigs' operation. Both patients recovered with conservative treatment. Ileus has not previously been described as a complication to hypotension induced by spinal analgesia, and it cannot be decided whether the surgical procedure or the hypotensive technique was responsible in our two cases. No cardiovascular or cerebral complications have been encountered. Kidney function has been present on the day of operation in all patients. One case of secondary haemorrhage has been observed (Case No. 13), where a haematoma

Table I.
19 patients operated on under hypotensive spinal analgesia.

Case no.	Sex	Age	Type of operation	Spinal analgesic agent		Systolic blood pressure			Duration of hypotension min.	Blood transfusion		Complications
				nupercaine mg	tetracaine mg	preoperative	during operation	at end of operation		during operation	after operation	
1	f	46	Meigs' op.	11		130	65	110	125	2	0	
2	f	26	—	11.5		120	65	100	100	2	0	
3	f	35	—	11.5		120	65	110	120	2	1	
4	f	30	—	11.5		115	70	100	95	2	0	
5	f	38	—	11		130	60	100	70	2	0	paralytic
6	f	41	—	11		130	60	100	120	2	0	ileus
7	f	46	—	10		170	70	140	70	1	1	
8	f	40	—	11		115	65	100	100	2	1	paralytic
9	f	31	—	11		115	60	90	90	2	0	ileus
10	f	39	—	12		120	85	130	90	2	0	
11	f	41	—	10		140	55	105	190	3	0	
12	f	49	—	10		140	65	120	90	2	0	
13	f	39	—	10		120	60	110	100	2	0	secondary
14	f	36	—	10.5		135	70	100	90	2	1	haemorrh.
15	m	48	expl. lap.		15	140	60	70	50	0	1	
16	m	58	colon resect.		20	160	55	100	60	1	0	
17	f	70	abd. anal. resect. of rectum		16	155	50	95	55	1	0	
18	f	72	extirp. of rectum		20	150	60	105	25	1	1	
19	f	28	extirp. tum. retroperiton.	10		110	75	100	75	1	0	

formed in the right parametrium became infected and had to be emptied by the vaginal route.

DISCUSSION

Little (1955), in his statistical survey of 27930 operations with induced hypotension, states that the postoperative morbidity of the hypotensive technique itself is 1 in 31 and the mortality 1 in 291. He does not mention the incidence of complications following the different methods of inducing hypotension, but the majority of his material comprises either peripheral ganglionic block — 60 per cent — or high spinal analgesia with total sympathetic block — 34 per cent. These methods give identical reactions in the peripheral vascular system, (Hershey & al., 1954). Even if it is believed that the incidence of complications can be reduced with increasing experience, partly with the technique itself and partly in the preoperative selection of the patients, it must be realized that the use of induced hypotension constitutes — in Gillies' words — a "physiological trespass", and indications for application of the method should be narrow and carefully considered. Even in our small material we feel that our indications have been too liberal. It is, e. g., hardly justified to expose the patient to the added risk of induced hypotension when a resection of the colon or an operation for cancer of the rectum is contemplated, if the only major advantage is the saving of one or two bottles of blood. We still, however, consider use of the method indicated in cases where the end-result of the operation depends upon the prevention of oozing from the wound as in extensive gland dissections. Operations that are particularly apt to lead to life-threatening haemorrhage, such as intracranial aneurysms and operations on the large central vessels may represent another vital indication. Several other indications are mentioned in the literature, but many of these seem to rest mainly on the fact that the hypotensive technique renders the operation easier and more rapidly performed, an advantage that unfortunately is outbalanced by the increased risk that the method entails.

The basic theory which makes the use of a hypotensive technique permissible rests upon the fact that maintenance of the circulation is not directly dependent upon the systolic blood pressure, but on the preservation of the normal pressure gradient in the capillaries. This condition may be answered at the lowered blood pressure level, provided that the peripheral resistance, which mainly depends on the degree of contraction of the arterioles, is reduced by vasomotor paralysis. This may explain why experimental and clinical investigations into circulatory conditions and organic functions during and after the hypotensive period have, on the whole, given favourable results, in spite of the fact that local or general circulatory failure is the commonest cause of fatal complications from induced hypotension. When inducing hypotension, the anaesthesiologist can never know for certain whether the patient's peripheral circulatory system has not in some area lost so much of its resilience that the resistance to circulation at the reduced blood pressure may prove too great. The risk of thrombosis and hypoxia under these conditions is evident. It can hardly be a surprise that Little finds the most serious complications at blood pressures below 80 mm Hg.

The risk of a sudden cardiovascular collapse is also increased with diminishing blood pressure levels, particularly if the blood pressure drop occurs rapidly. Improved hypotensive technique should make this complication rarer.

It can be concluded that the method is contraindicated in the presence of myocardial disease, manifest arteriosclerosis, and malignant hypertension, as well as diseases that impair the transportation of oxygen from the lungs to the peripheral tissues.

Secondary haemorrhage is the complication most frequently met, but does not represent as great a risk to the patient as the above-mentioned circulatory complications. It may, however, sometimes invalidate operative results. Careful haemostasis and not too sudden elevation of the blood pressure towards the end of the operation, followed by scrutiny of the surgical field should improve the chances of a successful result in this respect.

If in present day anaesthetic practice it is considered justifiable to induce hypotension, vasomotor paralysis must be the method to be preferred. The main reason why we have preferred total subarachnoid sympathetic block to the specifically acting ganglionic blocking agents, is the greater certainty with which hypotension can be induced by this method, also in young individuals, who in 10 to 15 per cent of cases are refractory to attempts at induced hypotension by means of these drugs (Enderby 1952). Another fact that speaks in favour of spinal analgesia in this context is the reduced amount of general anaesthetic needed at operations on the lower two thirds of the body.

Furthermore, should renal ischaemia accidentally occur during the hypotensive period, kidney function may be impaired. This will not influence the duration of hypotension, when spinal analgesia is used. If, on the other hand, specific hypotensive agents are employed, such a condition may lead to undue prolongation of the hypotensive period, since the latter agents are at least partially eliminated through the kidneys.

The main argument against the spinal technique is that against spinal analgesia as such. For this reason Bromage (1950) advocates sympathetic block by means of epidural analgesia, a method which has given good results in his hands.

In chest surgery and particularly in surgery on the head and the neck, the analgesic and muscle relaxant actions of spinal analgesia can not be utilized to the same advantage.

Even if the anaesthetist does not object to the use of continuous spinal analgesia — and the frequent neurological sequelae that it entails — he must realize that spinal analgesia is inferior in flexibility to Arfonad, a specially acting ganglionic blocking agent, as a means to hypotension.

SUMMARY AND CONCLUSION

The physiological background and the technique of induced hypotension by spinal analgesia is outlined.

The method has been employed in 19 cases of major surgery. One case of secondary haemorrhage was observed. No other complications could with certainty be ascribed to the hypotensive technique. The indications and contraindications are discussed, and the inherent dangers of the technique is stressed.

It is concluded that spinal analgesia represents a useful method of inducing hypotension, especially on the lower two thirds of the body.

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THE SIGNIFICANCE OF THE SPLEEN FOR SURVIVAL AFTER TOTAL-BODY X-IRRADIATION

EXPERIMENTAL INVESTIGATIONS ON MICE WITH LEAD-SHIELDED SPLEEN

By SIGVARD KAAE and OLAF PETERSEN

Jacobson et al. published in 1949 the results of some animal experiments with total-body X-irradiation, using doses in the lethal range. 10—12 week old female mice of the CF-1 strain were used as experimental animals. With the spleen operatively exposed and externalized on the abdomen, and then protected during irradiation by means of an approximately 6 mm thick layer of lead, the dosis media letalis (LD_{50}) was found to be approximately 1100 r. In a control group treated in exactly the same manner, but without lead protection of the spleen during the X-irradiation, the LD_{50} was approximately 600 r.

No protective effects of a similar order of magnitude could be demonstrated by the lead shielding of other organs, for example the liver, lungs, small intestine, kidneys, or regions of the experimental animals (head, lower extremities) (Jacobson et al. 1951).

Corresponding conditions are found when using other experimental animals (rats, guinea-pigs, rabbits), but the protective effect of covering the spleen is, however, less (Jacobson et al. 1950, Gershon-Cohen et al. 1951, Friedell & Salerno 1954).

The survival percentage is the same when the spleen vessels are clamped during the irradiation and freed immediately afterwards (Jacobson et al. 1951), just as an extirpation of the lead-protected spleen as early as 5 minutes after the irradiation produced no significant reduction in the survival percentage (Jacobson et al. 1952). Implantation of spleens or injection of spleen homogenate in the peritoneum within 2 hours of total-body irradiation, has likewise been shown to have a protective effect (Jacobson et al. 1951, Cole, Fishler, Ellis & Bond 1952).

In the course of 1951—1952 we have re-examined a number of these experiments at the Radium Centre, Copenhagen, and the results are briefly referred to in what follows.

Male mice of the Dba strain were used, inbred at the Radium Centre through 40 generations. Mice of weight 19.5—20.5 gm were selected.

The spleen is surgically exteriorized under Nembutal anaesthesia, and after severing the vessels to the lower pole of the spleen, without

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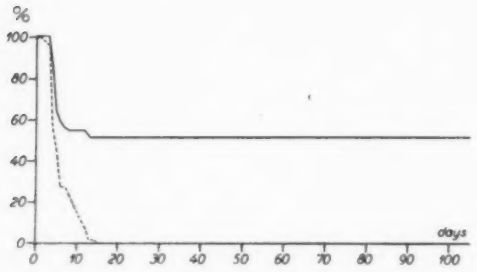

Fig. 1.
The survival percentage after total-body X-irradiation, dose: 640 r.
——— with lead-protected spleen (44 mice)
— — — without lead-protected spleen (46 mice)

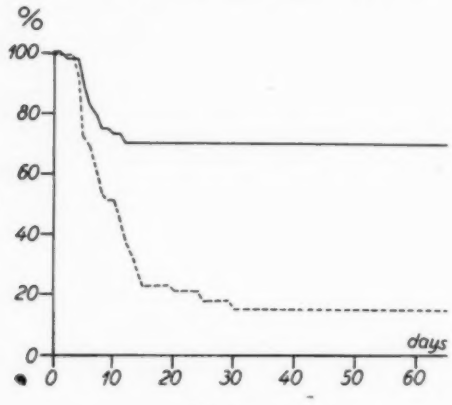

Fig. 2.
The survival percentage after total-body X-irradiation, dose: 585 r.
——— with lead-protected spleen (40 mice)
— — — without lead-protected spleen (39 mice)

ligature, it is covered with a piece of gauze soaked in physiological saline, and in the case of the test animals placed in a lead box of 10 mm wall thickness. The box is placed by the side of the mouse, and the pedicle of the spleen led out through a 2 mm wide slit in the side of the box. The spleen of the control animals is exposed in a similar manner, placed in gauze soaked in saline at the side of the animal, but without lead protection. One test animal and one control animal are irradiated in the same session, fastened side by side in full anaesthesia on a cork plate.

The X-irradiation is given with 180 kV, ½ mm Cu-filter, 50 cms distance, 12mA, half-value-layer 0.9 mm Cu. The doses, calculated at the centre of the animals, inclusive of secondary radiation, were 640 r in the first group of experiments and 585 r in the second group.

The experiments involved equal numbers of mice irradiated with lead shielding of the spleen and control mice without lead protection of that organ. A few mice were omitted from the investigations on account of death from anaesthesia or technical accidents (spleen torn off during irradiation, extensive stasis of the spleen on account of clamping of the vessels).

The experimental results are shown in Figs. 1 and 2.

In the original plan of the experiments it was intended to observe the experimental animals up to their spontaneous death. On account of infection in the animal cages which started in March, 1952, an assessment had, however, to be made at that point, i. e., before the infection began to have an effect. In the first experimental group it was possible to follow the mice for 105 days, while in the other experimental group the animals could only be followed for 65 days. It will be seen that the majority of the mice died about 4—5 days after total-body irradiation. Some few mice died after 10—14 days. No mice died after 30 days in the period under consideration. Furthermore, it is clearly seen from the curves that there is a considerably greater survival in the groups with lead-protected spleen than in the control groups. In the first test group, where the dose was 640 r, the 30 day survival is 52 %, against 0 % in the control group. In the second test series, the 30 day survival is 70 %, against 18 % in the control group.

After irradiation of the spleen, its weight decreases considerably. The difference in spleen weight in mice irradiated with and without lead protection is seen in Figs. 3 and 4.

Fig. 3 shows the spleen weight at death after total-body irradiation with 640 r. Only those mice are recorded which died at the latest 15 days after irradiation, as all the control animals were dead by that time. In Fig. 4, the spleen weights at death after total-body irradiation with 585 r are compared both for mice which died early

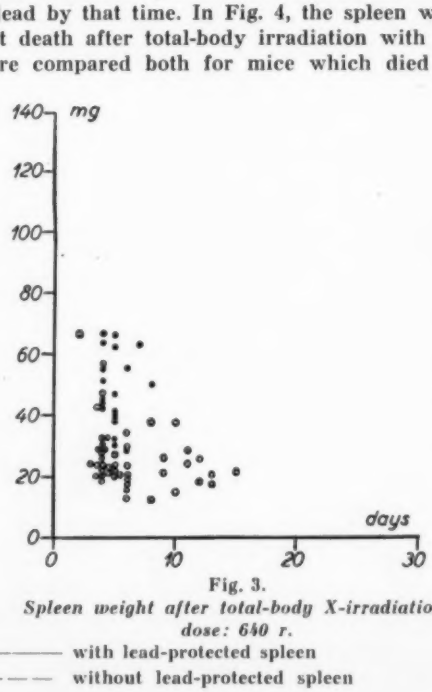

Fig. 3.
Spleen weight after total-body X-irradiation, dose: 640 r.
——— with lead-protected spleen
— — — without lead-protected spleen

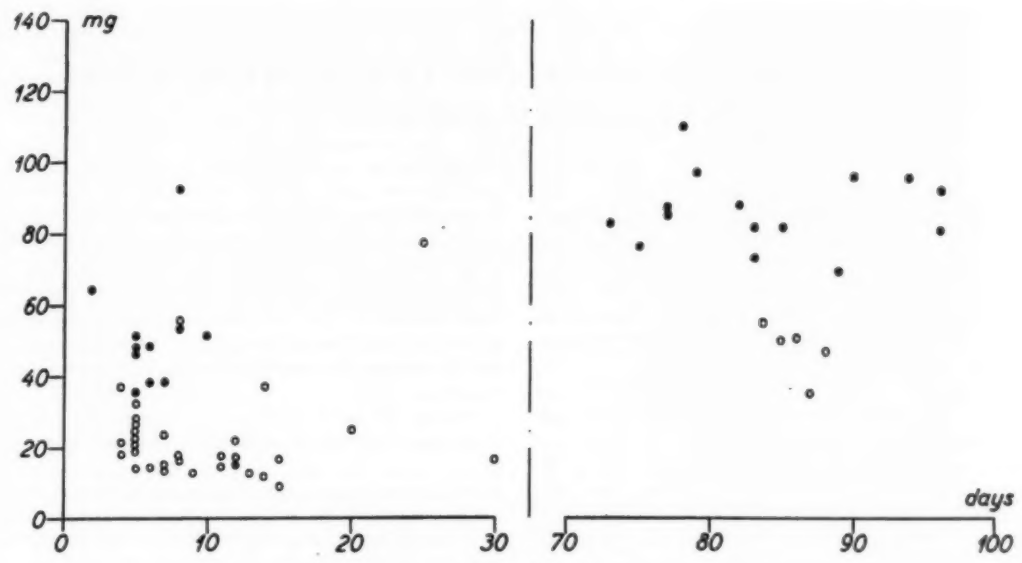

Fig. 4.
Spleen weight after total-body X-irradiation, dose: 585 r.
———— with lead-protected spleen
— — — without lead-protected spleen

(i. e., in the course of 30 days), and for mice which died late from infection (after 70 days).

The difference in spleen weight for test and control animals is clear, however both for those, with death at an early stage and for those animals which died late in the experimental period on account of infection.

The experiments in question confirm the assumption of Jacobson et al. that lead protection of the spleen clearly increases the chance of survival after X-irradiation. However, LD_{50} in our experiments lies at approximately 650 r, while Jacobson et al. found this value to lie at approximately 1100 r. This difference must presumably be due to the use of two different strains of mice.

Jacobson assumed already at an early stage that the cause of the increased survival under total-body X-irradiation, with lead-protected spleen, was a humoral factor (or factors) in the spleen, which stimulated the bone marrow. Experiments are being conducted at the moment in many parts of the world in an attempt to isolate this (or these) presumed effective factor(s). Cole, Fishler & Ellis (1955) have shown that it is a question of a non-dialyzable, unstable, thermolabile, radiation-sensitive substance bound to the nuclear fraction, presumably a desoxyribonuclein acid-protein complex.

Experiments with the implantation of spleen or the injection of spleen extract are of great interest. These experiments are so far the only ones in which an effective protective action has been obtained against total-body ionizing irradiation by measures put into effect after the irradiation.

SUMMARY

A brief review of the literature and the authors' own experiments with total-body X-irradiation of mice with and without lead-protection of the surgically exteriorized spleen are described. Very considerably increased survival rates were found in the groups with lead-protected spleen under total-body X-irradiation with doses around 600 r.

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METASTATIC CALCIFICATION IN A PATIENT WITH SALT-LOSING NEPHRITIS

By STEFFEN GJØRUP

Metastatic calcification is defined as abnormal deposition of calcium in previously healthy tissue in contrast to the dystrofic calcification seen in previously injured tissue; it has been described in connection with various diseases in which the serum is oversaturated with calcium and phosphorus.

The interest in the problem has been revived in recent years by the reports of metastatic calcification following excessive intake of milk and alkali in the treatment of peptic ulcer (3, 6, 8). In the latest report, Snapper et al. (6) present two additional cases and review this dietary etiology. They suggest that the excess alkali intake may be a more important factor in the development of the calcification than excess calcium ingestion.

This suggestion is supported by the observation of metastatic calcification developed during treatment of salt-losing nephritis with a high-bicarbonate diet (1, 4, 5, 7).

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Chief: *K. Brøchner-Mortensen.*

In the following, one additional case will be described of metastatic calcification in a patient with salt-losing nephritis developed during a period with high ingestion of alkali. The detailed case-history of the patient has previously been presented by the author with a short review of the literature concerning the salt-losing nephritis syndrome (2).

During the final stage of his disease the patient developed extensive metastatic calcifications.

The patient was a thirty-six-year-old man with a previous history of renal disease. The chief element in his disease was inability to retain sodium. During his stay in hospital his daily output of sodium in the urine averaged 470 meq. per 24 hours in spite of a low serum-sodium concentration. He was discharged from hospital in March 1954 and has been regularly examined during the following 19 months (Fig. 1) until his death in September 1955. He lived on a high sodium diet with a supplement in tablets of 15 g of sodium chloride and 8 g of sodium bicarbonate daily. Although the renal insufficiency was clearly demonstrated through an average serum-urea concentration of 200 mg per 100 ml, the patient continued to work as a clerk. About 8 months before his death

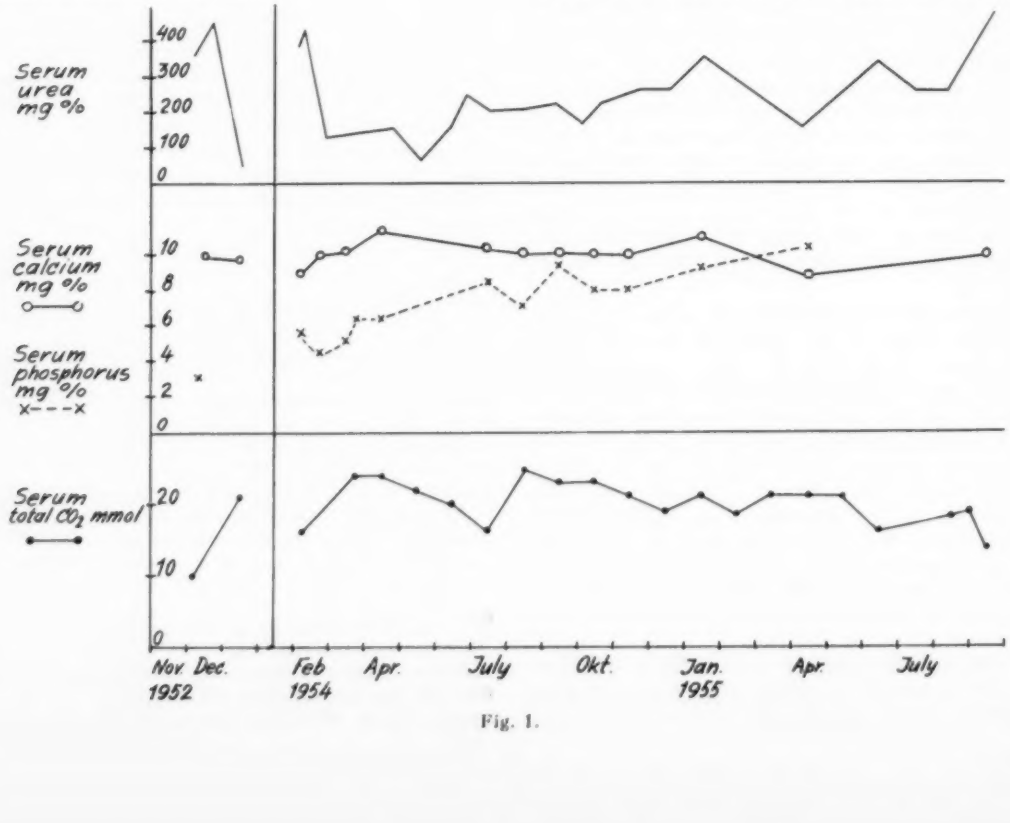

Fig. 1.

he developed a rapidly progressive anemia partly accentuated by heavy attacks of nose bleeding, and he was regularly treated with transfusions. After each bleeding the renal insufficiency increased and was only partly restored by the transfusion treatment.

About two weeks before his death he was re-admitted to the hospital. He now complained of severe pain in both legs. X-ray examinations of the extremities revealed no explanation of the pain, but disclosed the astonishing picture of a diffuse calcification of the vessels, the picture resembling that of an arteriography (Fig. 2 & 3). Further examinations, including the skull and vertebral columna, disclosed the intravascular calcifications to be widespread throughout the body.

The patient's condition rapidly deteriorated and he died in convulsions in terminal uraemia (serum urea 370 mg per 100 ml).

Necropsy findings.

The arteries: the distal part of the aorta showed slight, atheromatous degeneration but no calcification. The smaller branches of the iliac and mesenteric arteries, the arteries of the extremities and the arteries of the meninges were all tortuous, stiff and brittle. Histological examinations demonstrated only slight atheromatous degeneration, but large calcium deposits were found in the media. These changes were also noted in the branches of the vertebral and carotid arteries of the brain.

The heart was enlarged (520 g). There was a recent fibrinous pericarditis and numerous small hard nodules in the mitral commisure. No calcifications of the coronary arteries. The myocardium was normal on microscopy.

The lungs: on the entire cut surface there were small hard nodules which histologically appeared to be interstitial deposits of calcium.

The kidneys were of about normal size. The capsules stripped without difficulty. On the surfaces, both kidneys were coarsely granulated and covered with small cysts, which on the cut surface were seen partly to intrude into the renal parenchyma. Histological examinations of the two kidneys were identical, showing widespread interstitial fibrosis, varying degrees of glomerular degeneration — some glomeruli were totally hyalinized and some were quite normal — and an overall tubular degeneration both in the proximal and the distal segments. The renal arteries were unchanged.

The adrenals had a total weight of 30 g. The histological structure was normal and no adenomas were found.

The parathyroids: all four glands were enlarged. The sections showed an extraordinary degree of hyperplasia with increased number of oxyphil cells.

COMMENT

The recorded cases of salt-losing nephritis are only few and the nature of the disease is only partly understood. All authors, however, seem to agree that the failure to conserve sodium in a normal way is the most important feature of the disease. The early recognition of the sodium depletion and adequate treatment with sodium chloride and sodium bicarbonate is of overall importance to the patient.

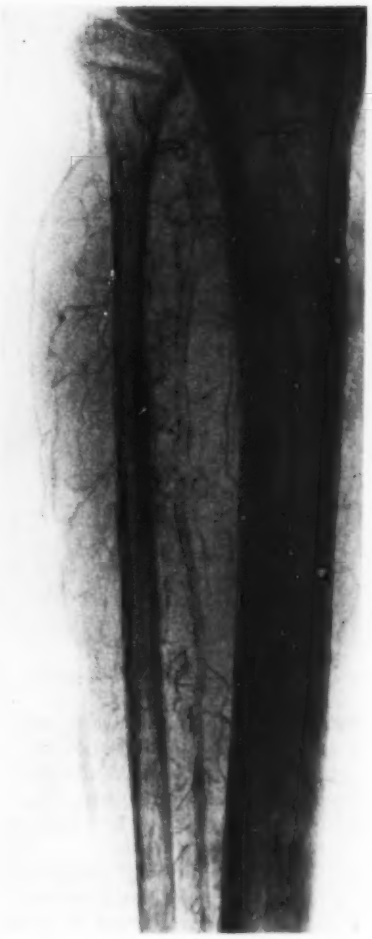

Fig. 2.

Besides the demonstration of an abnormal sodium metabolism, disturbances in the calcium metabolism have been reported in some cases (5, 7). The case published by Sawyer & Solez (5) and the case presented in this paper seem to be closely alike. In both patients extensive calcifications were found in the smaller arteries and also in the lungs. The observation of parathyroid enlargement reported in Thorn's two cases (7) and in this case points to a more general disorder of the calcium metabolism.

Whether this is primary or secondary to the renal disease is open to discussion. In our case the concentration of calcium and phosphorus in the serum was followed through 19 months. The calcium concentration remained normal, whereas the serum-phosphorus concentration gradually increased. The hyperphosphatemia secondary to the increasing renal impairment may be the cause of the parathyroid hyperfunction.

The altered calcium metabolism may be secondary either to the final stage of the disease in itself or to the treatment induced. Common to the

Fig. 3.

two patients with the most heavy calcificaions (that of Sayers & Solez and our case) is the ingestion of large amounts of alkali over a long period. Also Thorn's case No. 1, where the arterial changes were only small, had been treated with large alkali doses.

In our patient the arterial calcifications are known to develop during the bicarbonate treatment. They were not observed in March 1954 (before the alkali treatment was started) on an X-ray examination of the same regions where they were detected in August 1955. This points to the alkali treatment as an important factor.

A similar syndrome of metastatic calcification resulting from prolonged treatment of peptic ulcer with milk and alkali also stresses the alkali as important. The clinical and post-mortem findings in the milk-alkali treated patients are closely alike to those of the patients with salt-losing nephritis. Both groups have increased concentration of phosphorus in the serum; in the former group probably due to the high phosphate content of the ingested milk and in the latter group due to renal insufficiency.

The combination of hyperphosphatemia and excessive alkali intake seems to be the circumstance under which metastatic calcification may occur. The reason why the abnormal precipitation is mainly situated in the arteries is obscure.

SUMMARY

In a patient with salt-losing nephritis severe metastatic calcifications were seen to develop during the final stage of the disease. The treatment of the renal disease with a high-alkali diet is discussed as a possible causal agent.

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CHRISTMAS FACTOR DEFICIENCY AND DECREASED CAPILLARY RESISTANCE IN A FEMALE WITH HAEMORRHAGIC DIATHESIS

By KNUD-ERIK SJØLIN and AAGE VIDEBÆK

Cases of haemorrhagic diathesis in women caused by defects in the plasma thromboplastin system and by an increased capillary fragility, have been reported recently by Merskey (1951), Alexander & Goldstein (1953), Larieu & Soulier (1953), and Greveld, Jordan, Punt & Veder (1955). The following is a report of a haemorrhagic diathesis in a woman. The disorder was found to be caused by a decreased content of Christmas factor in plasma and a decreased capillary resistance.

CASE REPORT

Family history. No relatives have ever showed any signs of haemorrhagic disorders. Her father died at 38 years of cerebral hemorrhage and uraemia following chronic nephritis of at least 10 years' duration. Her mother is 42 years old and suffers from a congenital luxation of one hip. A female cousin has a congenital luxation of both hips. Three siblings as well as 5 half-sisters and half-brothers are healthy. (See the pedigree in Fig. 1).

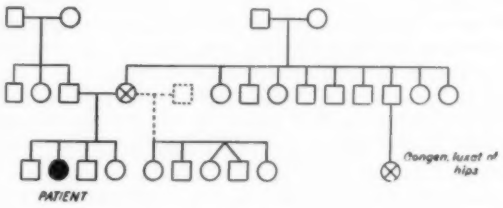

Fig. 1.
Pedigree.

Case history. The patient was born at term after a normal delivery. There was no melaena neonatorum and no haemorrhage from the umbilical cord. At the age of 8 days several haemorrhagic bullae appeared on the skin. At the age of 12 months she was admitted to hospital because of purpura and epistaxis; the thrombocyte count was then 296,000. Dentition was always complicated by protracted bleeding, and haemorrhage from the gums and oozing epistaxis were very often observed. The purpura occurred only occasionally. Scratches continued to bleed for a long time. At the age of 9 years one knee joint became very swollen and tender following an injury. Her first menstruation continued for 25 days and the haemoglobin concentration decreased to 5.3 g per 100 ml. Her second menstruation started two months after the beginning of the first and continued for 24 days in spite of several blood transfusions. She was then admitted to hospital again.

Clinical findings. The nearly full grown 13 year-old girl had a height of 156 cm and a weight of 45 kg. She had oozing bleedings from the gums and a small haemorrhage in the oral mucous membrane but only a single sugillation and no petecchiae were observed. The nasal mucus was slightly stained with blood. Further clinical examination did not disclose anything abnormal apart from extensive caries. In particular, there were no regressive joint lesions.

Laboratory findings. Mantoux and Wassermann tests were negative. The urine contained no protein, glucose or blood. Blood pressure: 125/60 mm. ECG was normal. X-ray examination showed normal conditions in the chest and a spleen of normal size. Haemoglobin: 6.6 g per 100 ml, and serum iron: 31 μg %. WBC:

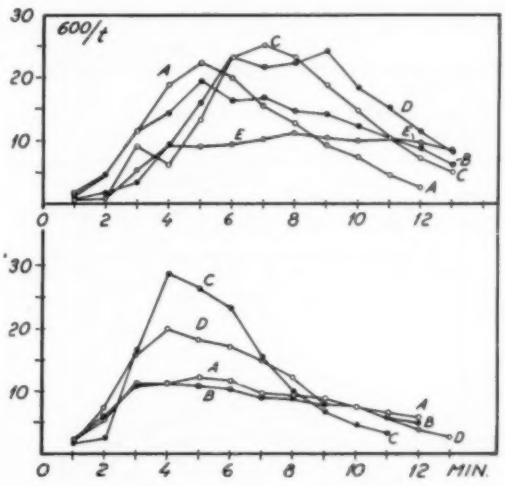

Fig. 2 (above).
The thrombin generation in 4 normal plasma samples (A-D) and in the patient's plasma (E).
Abscissa: Reaction time in minutes, i. e., minutes after recalcification of the citrate plasma.
Ordinate: Thrombin concentration expressed as reciprocal clotting times of fibrinogen solutions: 600/t (in seconds).

Fig. 3 (below).
The thrombin generation in the patient's plasma after addition of various plasma samples: A) from a patient with Christmas disease, B) from a patient with deficiency of both antihaemophilic factor and Christmas factor, C) from a patient with classical haemophilia (antihaemophilic factor deficiency), D) after addition of serum from a patient with classical haemophilia. Abscissa and ordinate as in Fig. 2.

(From the Biological Institute of the Carlsberg Foundation, Copenhagen; the Institute of Human Genetics, University of Copenhagen, and the Medical Department A, Rigshospitalet, University of Copenhagen, Denmark).

3,500; differential count was normal. Serum bilirubin: 0.6 mg %; thymol turbidity test: 0.05 (normal); Takata-Ara test: negative. Thrombocytes were on two occasions: 184,000 and 207,000. The bleeding time was repeatedly found from 2 to more than 15 min. (Duke). Coagulation time of whole blood: 3 min. (Lee & White). The capillary fragility test was strongly positive and varied from 30 to 65 petecchiae (100 mm Hg pressure in 3 minutes). Prothrombin-proconvertin time: 105 % (Owren, 1949, Astrup, Müllertz & Hansen, 1951). Quick prothrombin time: 90 %. Fibrinogen in plasma: 0.24 % (Gram, 1921). Electrophoretic examination of serum-proteins (Antweiler): Albumin + alfa$_1$: 70.0 %; alfa$_2$: 9.8 %; β: 8.1 %; γ: 12.1 %. Serumprotein, total (refractometrically): 5.7 %. The thrombin generation test was performed as described before (Sjølin, 1956). Fig. 2 shows the thrombin generation in the patient's citrate plasma (E) compared with four normal controls (A-D). The thrombin concentration never reached normal values. The addition of 0.2 ml plasma from a patient with Christmas disease (Fig. 3 A) or from a patient with a deficiency of both AHF and the Christmas factor (Fig. 3 B) did not improve the thrombin formation. It became normal after the addition of 0.2 ml citrate plasma from a patient with classical haemophilia (Fig. 3 C) and after the addition of 0.2 ml thrombin-free serum from another patient with classical haemophilia (AHF deficiency) (Fig. 3 D). Fig. 4 B shows the thrombin generation

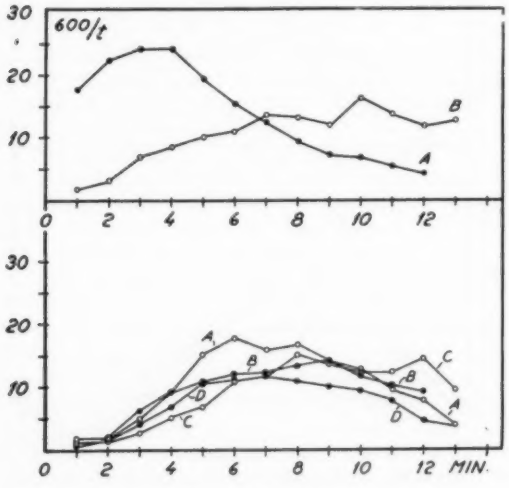

Fig. 4 (above).
The thrombin generation in the patient's plasma (B). Curve A shows the thrombin generation after addition of a preparation of Christmas factor. Abscissa and ordinate as in Fig. 2.

Fig. 5 (below).
Thrombin generation in the patient's plasma after transfusion of 450 ml blood (see text). The amount of transfused blood evidently was too small to make the thrombin generation normal.

in another plasma sample from the patient. If 0.2 ml Christmas factor preparation made according to Aggeler, Spaet & Byron (1954) was added to fresh plasma from the patient, the formation of thrombin became normal (Fig. 4 A). In Fig. 5 A-D the thrombin generation in the patient's blood immediately after transfusion of 450 ml blood (A), after 16 hours (B), after 40 hours (C), and after one week (D) is demonstrated. When 0.2 ml of the patient's plasma was added to 1 ml of plasma from a male patient with known Christmas disease (Fig. 6 A), there was an improvement of the thrombin generation, but it did not become normal (Fig. 6 B). The thrombin formation first began after 4 minutes, and the maximum thrombin concentration was obtained after 9 minutes. Fig. 7 A shows the thrombin formation in a control plasma. Fig. 7 B shows the thrombin for-

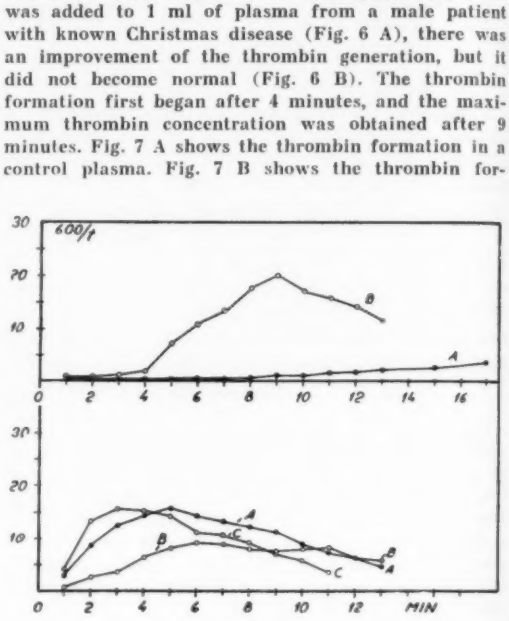

Fig. 6 (above).
Thrombin generation in a patient with Christmas disease (A). After addition to this plasma of plasma from our patient (curve B) the thrombin formation was still considerably delayed.

Fig. 7 (below).
The influence of platelets from our patient on the thrombin generation in a normal platelet-poor plasma sample (see text).

mation in the same plasma after centrifugation for 15 min. with 2000 r. p. m. for removal of the majority of the platelets. The thrombin generation was delayed and the maximum concentration decreased noticeably. After the addition of 0.4 ml of a platelet suspension from the patient the centrifuged control plasma returned to normal (Fig. 7 C). The normal plasma used in this experiment gave a lower thrombin generation curve than in most cases.

DISCUSSION

The results suggest that the patient has the same defect in her plasma thromboplastin system as do patient's with Christmas disease. Disturbances in the prothrombin system could not be demonstrated. There was no indication of the presence of a coagulation inhibitor. The number of platelets was within normal limits and disturbances in the platelet function could not be demonstrated. Fibrinogenopenia could be excluded.

The addition of plasma from a patient with deficiency of both the antihaemophilic factor and the Christmas factor had no effect upon the thrombin formation. Neither did the addition of plasma

from a patient with Christmas disease improve the thrombin formation. Addition of plasma or thrombin-free serum from a patient with classical haemophilia, both of which contain Christmas factor, made the thrombin generation normal. The laboratory investigations were compatible with the diagnosis of Christmas disease, but in her family no cases of haemorrhagic diathesis were known. The deficiency in the Christmas factor content was apparently not complete, as the patient's plasma slightly improved the thrombin formation in plasma from a patient with true hereditary Christmas disease.

As mentioned above, a few similar cases of female haemophilia have been seen by previous authors. Alexander & Goldstein (1953) observed a five-year-old girl with haemorrhagic diatheses. Her twin brother died of haemorrhagic diathesis. The girl had prolonged clotting time which could be corrected by normal plasma. In addition, she had a prolonged bleeding time, uninfluenced by plasma transfusion. The AHF activity was found to be decreased. The capillary fragility was increased. Her mother had no haemorrhagic diathesis, but she had abnormal capillaries. The patient of Larieu & Soulier (1953) was a 6-year-old girl with bleeding symptoms from the age of 15 days: epistaxis, haematomas, haemarthrosis and mucous bleedings. The family history revealed nothing. The bleeding time was prolonged, the prothrombin consumption decreased and there was a deficiency of antihaemophilic factor in the plasma. Creveld, Jordan, Paul & Veder (1955) described a woman, aged 24 years, suffering from a haemorrhagic diathesis. The clotting time and the bleeding time were prolonged. The Rumpel-Leede phenomenon was strongly positive. There was a deficiency of antihaemophilic factor in plasma. The family history was negative. Probably the two female patients described by Merskey (1951) also belong to the same group of haemorrhagic disorders.

The first three cases mentioned have in common a reduction of the antihaemophilic factor and a deficiency in the vascular function. Our patient had also a disturbance in the vascular function, but instead of a deficiency of antihaemophilic factor, she had a reduction in the Christmas factor concentration. As far as we known, this condition has not been described before.

SUMMARY

A haemorrhagic diathesis in a 13 year old girl was found to be due to a Christmas factor deficiency combined with a decrease in capillary resistance.

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THYMOL TESTS ON BLOOD DONORS

By NIELS FJELDBORG

Hepatitis is a very serious and not at all uncommon complication of blood transfusion.

In studies performed in this country in 1951, Steen Madsen reported an incidence of 0.4 per cent of hepatitis carriers. In studies on healthy carriers who had transmitted hepatitis to others, Ginzburger et al. (1951) revealed evidence of hepatitic disease by the thymol and cephalin liver-function tests.

In order to study the possibility of disclosing hepatitis carriers among blood donors, we have performed thymol tests on 501 subjects in relation to donation at the Aarhus County Hospital. The studies extended over five months, and the 501 donors were selected in such a manner that all subjects who had previously had clinically recognized hepatitis were excluded.

The thymol turbidity test was carried out according to the method of Shank and Hoagland (1946). Thymol turbidity exceeding ten units were regarded as pathologically elevated, and portions of blood with these values were

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Table 1.

Thymol turbidity units:	3	4	5	6	7	8	9	10	11	12	13	14	15	18
Number of donors:	11	35	122	152	58	38	55	10	4	8	4	2	1	1

normally discarded. However, in four cases in which transfusion was urgently required, blood with a thymol turbidity exceeding ten units was used before the result of the test became known.

The thymol-positive donors were subsequently summoned to appear for a detailed history-taking, repeated thymol test and, in addition, Takata-Ara test; at this second examination the donors were instructed to appear in the fasting state.

RESULTS

The results of the first thymol turbidity test in the 501 donors were as shown in Table 1.

The thymol turbidity exceeded ten units in twenty of these donors. Of the portions of blood donated by these subjects, sixteen were discarded, while four had already been used in urgent cases.

Of the twenty thymol-positive donors, seventeen appeared for the second investigation from one to eighteen weeks after the first test on donation; one appeared after the lapse of twenty-seven weeks, whereas one failed to return, and another had his history recorded but was not subjected to the tests.

At the second examination where the donors appeared in the fasting state, the thymol and Takata-Ara tests showed normal values in all cases. None of the individuals examined had had jaundice or been indisposed in the meantime.

Inquiry to the general practitioners knowing the four patients who had been given thymol-positive blood revealed that jaundice had not developed in any of these patients from five to seven months after the blood transfusions.

CONCLUSIONS

1. Thymol turbidity tests performed on a series of 501 normal non-fasting blood donors showed a normal Gaussian distribution curve with the peak at six units; minimum value three units and maximum value eighteen units.

2. The individuals whose thymol value exceeded ten units at the first test showed normal thymol and Takata-Ara reactions in the fasting state at a second examination.

3. The thymol turbidity test is of no practical value in revealing hepatitis carriers among blood donors, because the intake of fatty meals will give a high frequency of positive reactions.

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